Natural history and treatment of fibrous dysplasia of bone: a multicenter clinicopathologic study promoted by the European Pediatric Orthopaedic Society

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A multicenter study on fibrous dysplasia of bone (FD) was promoted by the European Pediatric Orthopaedic Society in 1999 in order to gain insight into the natural history of the disease and to evaluate current diagnostic and therapeutic approaches. We collected and reviewed clinical, radiographic, pathological, and molecular genetic data when possible, from a total of 64 cases diagnosed as either monostotic FD (MFD), polyostotic FD (PFD), or McCune–Albright syndrome (MAS), evaluated or treated in 11 participating centers. Results from the initial analysis of the series indicate five main points: (1) Significant diagnostic pitfalls affect the diagnosis of MFD and, to a lesser extent, PFD in orthopedic centers and allied radiology and pathology facilities, which may be circumvented by the adoption of stringent diagnostic criteria, and in some cases by the analysis of FD-associated GNAS1 mutations. (2) MFD carries a significant risk for fracture in the face of limited disease in the proximal femur, whereas its tendency to progress is restricted to a minority of cases, and long-term outcome is usually satisfactory, regardless of treatment, in non-progressive cases. (3) The profile of tibial disease, both in MFD and in PFD, is markedly different from that of femoral disease. (4) As expected, MAS patients have the most extensive disease and the most complicated course, regularly experience multiple fractures, and require adequate surgical treatment. It appears that conservative treatment of femoral fracture, or curettage and cancellous bone grafting, or fixation with screws and plates are not indicated for the treatment of femoral fractures in these patients and should all be discouraged. Internal fixation with intramedullary nails provides stabilization of extensively affected bones, and prevents further fractures and major deformities, and thus providing a better option both for acute and elective surgery in patients with extensive involvement of the femur or of other limb long bones. (5) Evaluation of patients with FD at orthopedic centers should include, but rarely does, a thorough evaluation of endocrine profile and phosphate metabolism, and proper pathological and radiographic assessment. *J Pediatr Orthop B* 12:155–177 © 2003 Lippincott Williams & Wilkins.

Journal of Pediatric Orthopaedics B 2003, 12:155–177

Keywords: fibrous dysplasia, McCune–Albright syndrome, GNAS1 mutations, orthopedic surgery, intramedullary nailing, pathology

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Sponsorship: This work was supported in part by grants from the MIUR and Telethon (E.1029) to P.B.

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Introduction

Fibrous dysplasia (FD) of bone may either occur as an isolated skeletal lesion (monostotic forms) or affect multiple skeletal sites (polyostotic forms) [1,2]. In addition, single or multiple endocrinopathies may concur with FD of bone and cutaneous hyperpigmentation in the classical triad of the McCune–Albright syndrome (MAS) [3–7]; whereas the term Mazabraud's syndrome is used to note the combination of FD of bone with myxomas of skeletal muscle [8,9]. Fibrous dysplasia of bone is a genetic, non-inherited disease caused by activating mutations of the GNAS1 gene, encoding the α subunit of the stimulatory G protein Gs [10–12]. The mutations occur post-zygotically, resulting in a somatic mosaic state, and cause the generation of excess cyclic AMP in mutated cells [10,12–14]. It was recently recognized that FD of bone expresses the impact of the GNAS1 mutations in cells of osteoblastic lineage, such that each FD lesion can be seen as the result of abnormally functioning osteogenic cells in the bone/bone marrow environment [15–19].

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DOI: 10.1097/01.bpb.0000064021.41829.94

FD remains a clinicopathologic challenge for many reasons. Although usually easily diagnosed, FD may present with clinical and radiographic features that may border with other benign fibro-osseous lesions of the skeleton, and (although rarely) may be confused with certain elusive types of malignancies. Furthermore, the highly variable constellation of radiographic changes observed at diagnosis or consultation remains poorly understood with respect to its prognostic significance and also as related to the specific pathologic nature of the underlying tissue changes. Cystic changes, excessive or reduced bone formation activity within the lesion and degree of mineralization all affect the radiographic appearance significantly [20,21].

Extensive and generalized forms of FD are crippling diseases, which may cause limping, multiple pathologic fractures, deformity, severe physical impairment and even confinement to a wheelchair. Multiple surgical approaches for the treatment of FD have been proposed [22–26], but careful evaluation of results is missing for many of them, and guidelines are not easily discerned in the maze of reports of surgical series which are unavoidably affected by the relative rarity of the disease. While medical treatments are being considered [27–30], and surgery cannot be expected to provide a curative type of treatment for a genetic disease, surgery remains a mainstay in the care of FD patients. Consideration of surgical options must of course include both the need to treat fractures in the most efficient way, and the need to correct, or, better yet, prevent, deformity through elective surgery. Both tasks depend upon an improved understanding of the natural history of FD lesions. By this we mean that an improved ability to predict the tendency of an individual lesion to grow and cause complication, or conversely to remain stable over time, cannot be easily predicted at this time. Likewise, the inherent structural characteristics of the lesional bone, which affect the outcome of any surgical procedure and the very spontaneous evolution of an untouched lesion, need to be better understood. Recent advances in the pathology of FD have started to elucidate aspects that are of critical clinical importance. For example, it was recognized that an inherent mineralization defect in FD affects the tendency of involved bone to bend and deform [16,20]. Additional insight may also come from an improved understanding of the varied radiographic appearance of FD lesions, which are rudimentary at best at the present time. This would include a distinction of potentially evolving from potentially stable lesions, an estimate of a lesion's biological age with respect to patient's chronological and bone age, and a prediction of the likelihood of events, including cysts, fractures, and deformity. Many of these objectives could only be achieved by a thorough correlation of radiographic, clinical and pathological findings in a significantly broad cohort of patients.

In 1999, the European Pediatric Orthopaedic Society (EPOS) promoted a multicenter study on fibrous dysplasia of bone with the aim of obtaining an overview of the diagnostic criteria, natural history of the disease, and value of different surgical approaches in use across Europe and beyond. The goals included consideration, when possible, of all aspects of the disease, from diagnostic pitfalls at presentation to molecular genetics, from pathological-radiographic correlation to evaluation of surgical approaches. An initial analysis of the data collected through the EPOS study is presented here, whereas presentation and discussion of specific aspects and insights derived from the initiative will necessarily be the subject of future reports.

Patients and methods

Study design and inclusion/exclusion criteria

The criterion for inclusion was given simply by a diagnosis of either monostotic FD, or polyostotic FD, or MAS, made on clinical, radiographic or pathologic grounds in any of the prospective participating centers. Participating centers were asked to contribute, in addition to the patient demographics and clinical information embodied in a circulated questionnaire, the relevant imaging and histopathological material for review. The material was collected and analyzed in Rome, Italy. A total of 64 cases were contributed. Cases for which neither radiographic nor pathological material was available for review were excluded (Table 1).

Mutation analysis

Mutation analysis was conducted for 10 cases (Table 2). In most of these, surgery was performed at the University "Tor Vergata" or at the University "La Sapienza" of Rome, Italy, during the course of the present study. Retrospective material contributed by other centers was in most cases not suited for genomic DNA extraction. Genomic DNA was extracted (using the Qiagen DNeasy Tissue Kit; Qiagen Inc., Valencia, California, USA) from fresh bone tissue samples obtained at surgery in four cases, from fresh tissue from a bone biopsy in one case, from formaldehyde-fixed bone in one case, from paraffin-embedded bone in one case, and from paraffin-embedded ovarian tissue in one case. In one further case, genomic

Table 1 Contributed and accepted cases

Clinical form	Contributed cases	Accepted cases
MFD	32	23
PFD	12	10
MAS	20	20
Total	64	53

Eleven contributed cases (nine MFD, two PFD) were excluded for inadequate diagnosis. MFD, monostotic fibrous dysplasia; PFD, polyostotic fibrous dysplasia; MAS, McCune–Albright syndrome.

Table 2 Mutation analysis

Patient	Material analyzed	Genotype
MAS 4	Bone tissue, fresh	R201H
MAS 5	Bone tissue, fresh	R201H
MAS 7	Peripheral blood leukocytes	R201H
MAS 8	Ovary, paraffin-embedded tissue	R201H
MAS 9	Bone, paraffin-embedded tissue	R201H
MAS 10	Bone tissue, fresh	R201H
MAS 11	Bone cell culture	R201C
MAS 13	Bone, formaldehyde fixed tissue	R201H
Non-MFD	Bone tissue, fresh	R201
MAS 14	Bone biopsy, fresh	R201C

MAS, McCune–Albright syndrome; MFD, monostotic fibrous dysplasia.

DNA was extracted from peripheral blood leukocytes. A target sequence of the GNAS1 gene including the R201 codon was amplified by the polymerase chain reaction (PCR) using the following primers: 5′-TGACTATGTGCCGAGCGA (sense) and 5′-AACCATGATCTCTGTTATATAA (antisense), and the Taq Gold DNA polymerase (Perkin Elmer, Norwalk, Connecticut, USA). After a denaturation step for 15 min at 95°C, the target 300 base pair sequence was amplified for 35 cycles at 95°C for 30 s, at 55°C for 30 s, and at 72°C for 30 s, followed by 7 min of final extension at 72°C. The PCR product was purified (Promega Wizard PCR Preps DNA Purification System, Madison, Wisconsin, USA) and then sequenced using dRhodamine dye-terminator cycle sequencing with Ampli Taq and the Perkin Elmer Applied Biosystem 377 Automated sequencer (Perkin Elmer, Norwalk, Connecticut, USA).

Review of histopathology

Histological material was reviewed to assess adequacy of (1) the histological material used for diagnosis, (2) the handling and processing of the material for diagnostic purposes, and (3) the diagnosis itself. In addition, histological material was collected for the purpose of investigative pathology and radiographic-histological correlation, which are not, however, discussed in detail in the present report due to space constraints.

Review of imaging material

Radiographic and bone scan material was reviewed jointly by orthopedic surgeons and pathologists participating in the study. The goal of the review was to establish accuracy of diagnosis, to complement clinical evaluation, and to sort out radiographic findings that could be informative as to evolution, progression, fracture risk, or classification of FD lesions.

Review of clinical data

Patients were then subdivided into separate cohorts corresponding to the accepted breakdown of clinical forms of FD: monostotic FD (MFD); polyostotic FD (PFD); polyostotic with endocrinopathies and skin pigmentation (MAS). Age at diagnosis, site of involvement, site and number of fractures, requirements for surgery, type of procedure employed, and outcome, were considered separately for each cohort.

Results

General remarks

Eleven of the contributed 64 cases were excluded due to misdiagnosis, as determined by review of histological, radiographic, and molecular genetic material. The accepted 53 cases included 23 cases of MFD (10 male, 13 female), 10 of PFD (five male, five female), and 20 of MAS (nine male, 11 female). The median age at diagnosis of skeletal lesions was 15.0 years for MFD, 11.0 years for PFD, and 4.5 years for MAS. Fracture prevalence (estimated as percentage of patients with at least one pathologic fracture) was 60.3% overall, 47% for MFD, 40% for PFD, 85% for MAS, and 70% for all polyostotic cases (PFD + MAS).

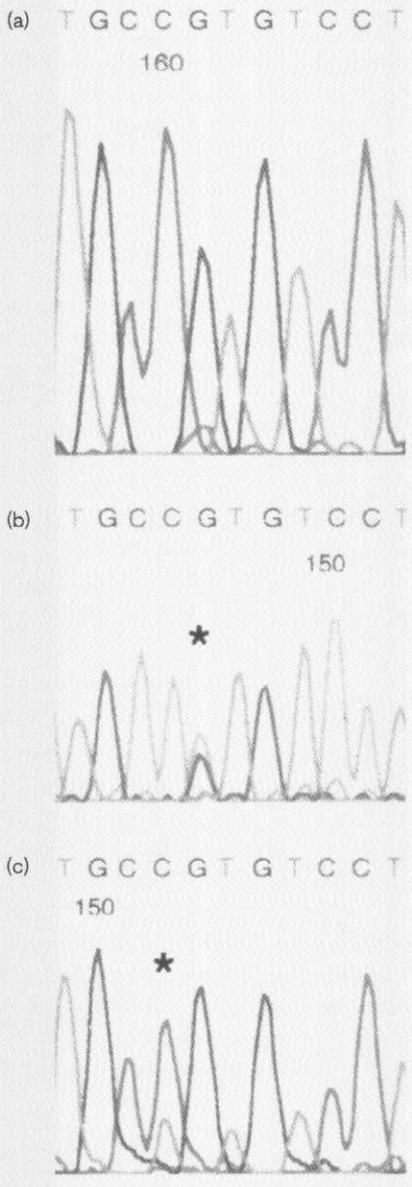
Mutation analysis

The results of mutation analysis are summarized in Table 2 and Figure 1. The mutation could be detected in different types of tissue samples including fresh, fixed, or paraffin-embedded bone, and paraffin-embedded ovary. In one case, it was possible to demonstrate the mutation in peripheral blood leukocytes. An R201 mutation was detected in nine cases (R201 H, seven cases; R201C, two cases). No mutation was detected in the remaining case, which turned out to represent ossifying fibroma of the jawbone. In this case (non-MFD in Table 2), mutation analysis was instrumental in establishing the correct diagnosis.

Histopathology

Review of clinicopathologic material, and in one case, availability of molecular genetics data, excluded nine of 32 cases of presumed MFD and two out of 12 cases of presumed PFD from the subsequent analysis of the natural history of FD. The excluded cases were found to represent unrelated conditions, or cases that were inadequately sampled histologically. This provided 28 and 16% rates of misdiagnosis for MFD and PFD, respectively. Lesions mistaken for MFD included non-ossifying fibroma (two cases), osteofibrous dysplasia, ossifying fibroma of the jawbone, fibrocartilaginous mesenchymoma, and hemangioma (Fig. 2). In three other cases, histologic material was inadequate for a diagnosis. An accurate diagnosis could be easily reached based on the understanding of bone pathology available to a general surgical pathologist in all cases but one. The latter case represented a benign fibro-osseous lesion of

Fig. 1



Sequence of the relevant fragment of the Gs alpha gene showing missense mutations in two fibrous dysplasia (FD) patients from the present series, and normal genotype in one. (a) The normal Gs alpha phenotype, R201, is specified by the CGT codon within the exon 8. The single base transition occurring in FD patients is revealed by a double peak (*). (b) G→A transitions are detected in patients bearing the R201H phenotype whereas (c) C→T transitions underlie the R201C phenotype.

the jaw (ossifying fibroma) in which the overall histological appearance could be mistaken for FD upon superficial evaluation. However, the adoption of diagnostic histological criteria that have been recently outlined for genuine FD – woven structure of the lesional bone, osteoblast retraction, Sharpey fibers along the edges of FD trabeculae (Fig. 3), pattern of distribution of FD trabeculae and its relationship to the specific bone involved – would have led to a correct diagnosis in this case as well (Fig. 4). Nonetheless, genomic DNA was extracted from the fresh lesional tissue and used for mutation analysis, which demonstrated the absence of R201 mutations of the GNAS1 gene (non-MFD in Table 2), contributing significantly to ruling out the diagnosis of FD, and emphasizing the importance of recognition of even subtle histopathological features of FD. Conditions mistaken for PFD were Ollier's disease in one case, and skeletal angiomatosis in one case. Radiographic findings were diagnostic for each condition, as were histological findings.

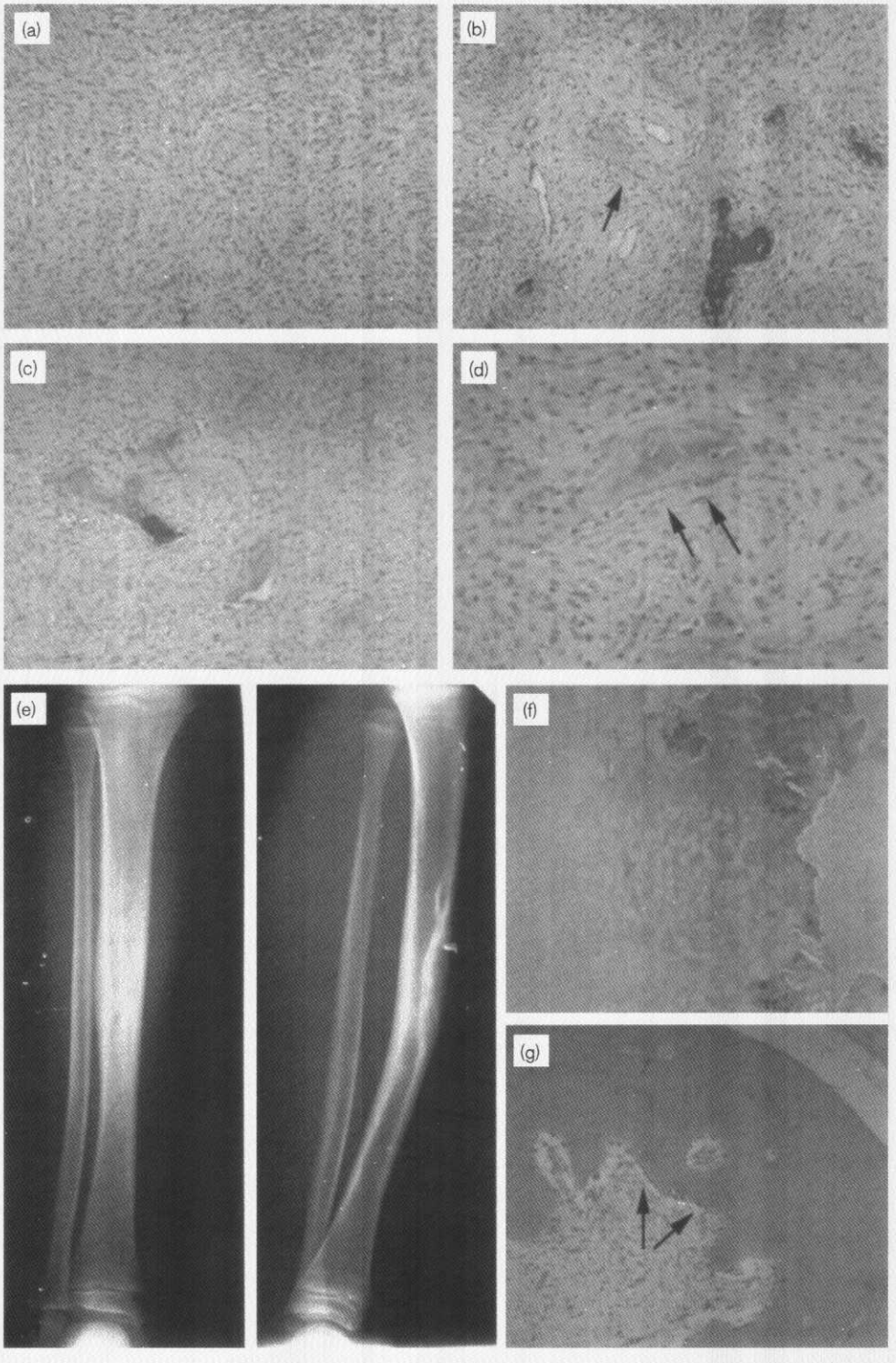
The histopathological picture observed in cases of true FD lesions (Fig. 3) was the same regardless of their occurrence as isolated or polyostotic lesions. Sharpey fibers, retracted osteoblasts, and a peculiar type of woven texture of the lesional bone matrix (so called combed bone) were recognizable in all cases. The extent of bone resorbing activity (osteoclast numbers) was highly variable across different cases. No information was available for most of them as to the general hormonal and metabolic profile of individual patients. Hence, it was impossible to determine the relative contribution of inherent properties of the FD tissue versus superimposed hormonal imbalances capable of affecting the rate of bone remodeling. Tunneling resorption (i.e. osteoclastic resorption of bone trabeculae from within) was a constant finding in all cases. Interestingly, we noted a high frequency of hemorrhagic changes within FD lesions. Dilated vascular channels engorged with blood were observed along the lesional bone trabeculae, along with foci of microscopic interstitial and peritrabecular hemorrhage, indicating an inherent high tendency of FD tissue to bleed. This finding was matched by the observation of unusually rich vascularity of FD tissue.

Monostotic fibrous dysplasia

The diagnosis of MFD was confirmed after review of available radiographic and pathological material in a total of 23 patients (Table 3). The patients had sought medical attention for fracture in four cases, and for limb swelling in two. Evidence of FD was an incidental finding at radiographic evaluation for unrelated reasons in two cases. In the remaining 15 cases, pain was the reason for initial orthopedic consultation. In cases with misdiagnosis of MFD, deformity was the initial complaint in one case, pain in three. No information was available about the remaining cases.

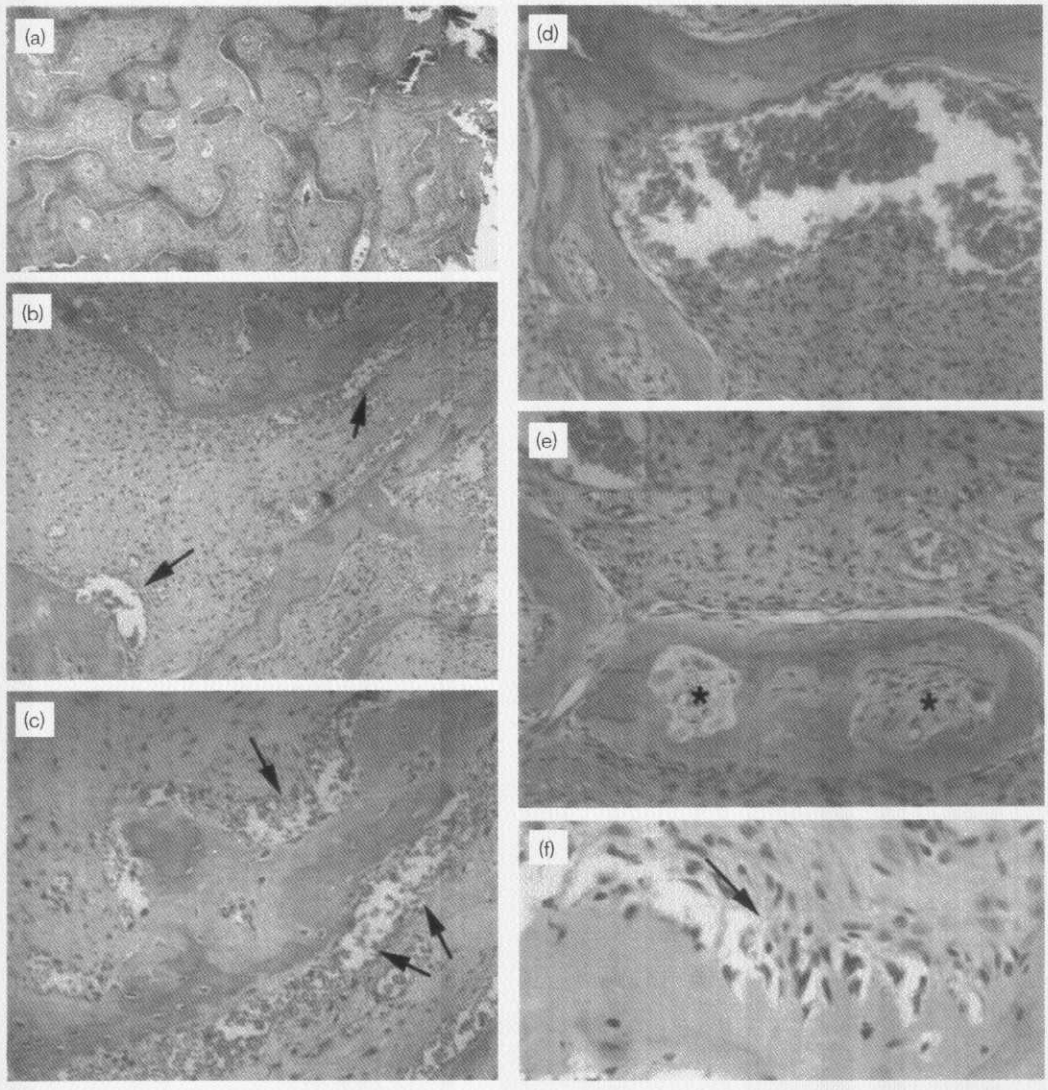
The femur was the most common site of involvement (14 of 23 patients), followed by tibia (four of 23), humerus (two of 23), rib (one of 23), clavicle (one of 23), and craniofacial skeleton (one of 23). Fractures occurred in 50% of the cases (seven of 14 femoral, two of four tibial,

Fig. 2



Histology of benign fibro-osseous lesions that were misdiagnosed as fibrous dysplasia (FD) in this series. (a,b) Non-ossifying fibroma. (a) Typical storiform (from Latin *storea*, meaning a mat) pattern. (b) Minor events of bone formation that occur in non-ossifying fibroma, particularly at the edge of lesions. Arrows point to deposition of genuine osteoid. (c,d) Osteofibrous dysplasia. This lesion, restricted to tibia and fibula, regularly features significant bone deposition in a fibrous background. Bone trabeculae are typically small, and may superficially resemble a 'Chinese writing' pattern as seen in FD, but are regularly bordered by plump, cuboidal osteoblasts. Osteofibrous dysplasia is genetically distinct from FD, and is not caused by GNAS1 mutations. (e) Radiographic appearance in the same case shown in (c,d). This lesion may be confused with a 'patchy' FD lesion. (f,g) Fibrocartilaginous mesenchymoma. Significant areas of hyaline cartilage (f), minor amounts of abnormal bone, and extensive fibrous tissue are observed. Osteoblasts (arrows in g) are of usual, plump/cuboidal morphology, clearly distinct from the abnormal osteoblasts seen in FD.

Fig. 3



Histology of fibrous dysplasia (FD). (a) Overall pattern of a true FD lesion. Irregular systems of abnormal bone trabeculae are interspersed in a fibrous background. The slit-like spaces seen along the profile of trabeculae correspond to vascular channels. (b–d) Dilated vascular channels engorged with blood along the trabecular profile in FD (arrows). These vessels are the likely source of intralesional bleeding, and of bleeding observed at surgery. (e) Tunneling osteoclastic resorption. Two erosion lacunae with osteoclasts excavating FD trabeculae from within are shown (*). (f) Typical appearance of a forming trabecular surface in FD. Note the prominent number of Sharpey fibers (bundles of collagen running perpendicular to the trabecular surface, arrow), among which retracted osteoblasts are seen.

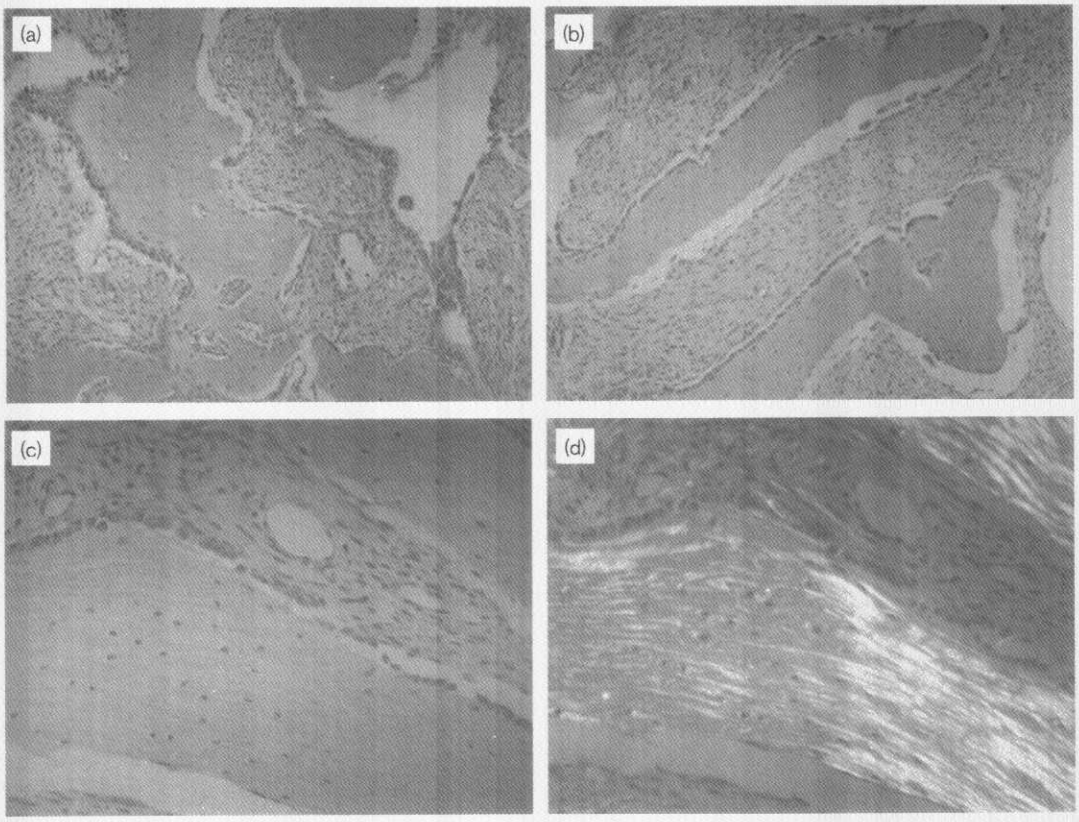
two of two humeral lesions), were never multiple, and were the presenting features in three patients with femoral and one patient with tibial disease.

Femur

The proximal third of the femur was involved in 13 cases, the diaphysis in two, and the distal third in one. The diaphyseal involvement occurred in isolation in one case, and as part of a single large cervicodiaphyseal lesion in the other. The distal third was involved as a 'skip' lesion (separate and distinct lesion distal to the principal one and separated from it by intervening normal bone) in a femur in which the larger lesion was seen in the upper third.

Six of 14 femoral lesions, all located in the proximal third, had a predominantly lytic radiographic appearance (Fig. 5a). Six of 14 lesions appeared as 'patchy' lesions with a non-homogeneous density, a ground-glass background, and a distinct sclerotic rim (rind) (Fig. 5b). Lesions of this type *per se* did not distort the bone contour. In one case, however, the non-deforming 'patchy' lesion was located within a bent metaphysis (shepherd's crook deformity). The single diaphyseal lesion had a

Fig. 4



Ossifying fibroma of jawbone that was diagnosed as fibrous dysplasia (FD) in this series. Histology clearly shows the rimming of lesional trabeculae by cuboidal osteoblasts, and (a–c) polarized light microscopy demonstrates the lamellar texture of the bone. (d) Sequencing of polymerase chain reaction amplified genomic DNA demonstrated a normal R201 genotype. This case highlights the diagnostic value of detection of Sharpey fibers and retracted osteoblasts in FD histological sections, and also the value of molecular genetics for confirming the diagnosis in cases that are perceived as borderline benign fibro-osseous lesions.

Table 3 Monostotic fibrous dysplasia

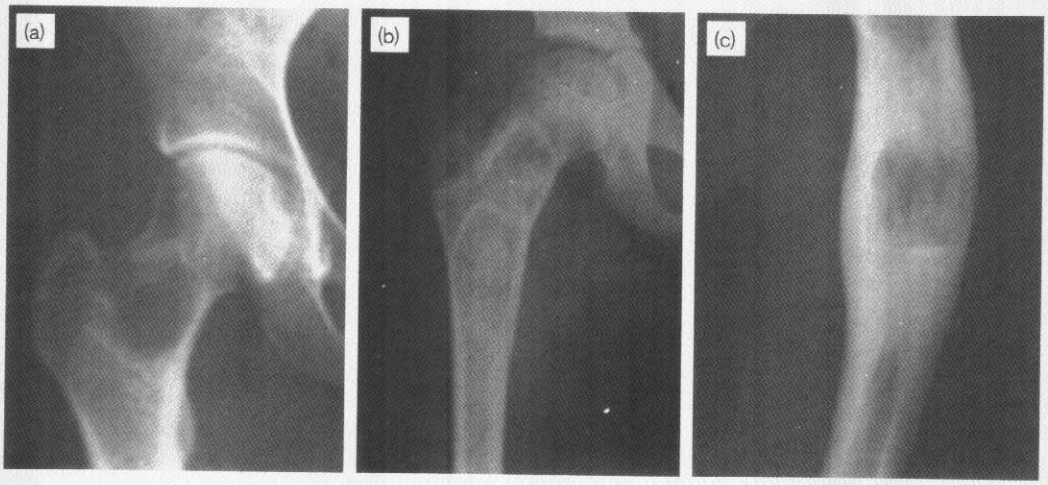
Patient	Age at diagnosis (years)	Sex	Site	Fracture
1	8	F	Femur	No
2	15	F	Clavicle	No
3	16	F	Tibia	No
4	8	M	Mandible	No
5	11	M	Femur	Yes
6	25	M	Femur	No
7	7	M	Femur	Yes
8	11	M	Femur	No
9	13	F	Humerus	Yes
10	19	F	Femur	No
11	23	M	Femur	Yes
12	9	M	Femur	Yes
13	14	F	Femur	No
14	19	F	Femur	Yes
15	42	F	Femur	No
16	32	F	Femur	No
17	9	M	Femur	Yes
18	7	M	Tibia	Yes
19	38	F	Tibia	No
20	21	F	Humerus	Yes
21	19	F	Femur	Yes
22	19	F	Rib	No
23	5	M	Tibia	Yes

F, female; M, male.

predominantly sclerotic appearance mimicking Brodie's abscess (Fig. 5c). The single cervicodiaphyseal lesion involved over half of the total femoral length, was markedly expansile (produced a 'blow-out' deformity of the bone contour) with marked thinning of the cortex, and displayed a complex internal trabecular network within a typical ground-glass background (Fig. 6a). The appearance of this lesion was in sharp contrast to the appearance of the more common lytic or patchy lesions. A large aneurysmal bone cyst developed within this lesion. Angiography demonstrated an unusually rich vascular supply suggesting an increased, tumor-like vascularity of the lesion prior to the development of the cyst (Fig. 6b).

A conservative approach (biopsy and observation, cast for fracture or stress fracture) was followed for five patients. Five patients were treated by curettage and cancellous bone grafting (CBG). In one case, the graft was resorbed and a second CBG was performed. In two cases, osteotomy in addition to CBG was required

Fig. 5



Representative images of radiographic patterns of monostotic fibrous dysplasia of the proximal femur. (a) Lytic lesion (radiolucent, not expanding the bone contour). (b) 'Patchy' lesion (localized, not expansile, with varied internal density and a distinct rind). (c) Unusual sclerotic lesion with an internal area of lucency, reminiscent of an abscess of Brodie.

to correct deformity (in one case, a coxa vara deformity developed following the initial CBG). The aneurysmal bone was treated by resection and use of a vascularized fibular bone graft along with internal fixation (Figs. 6c,d). All other patients were treated by application of Ender nails, or screws, or sliding screwplates or bladeplates.

The long-term prognosis of femoral lesions was uniformly good, and radiographic evidence of stabilization of the lesion was ultimately obtained in all patients, regardless of treatment. A reasonable preservation of hip function, and an improvement of symptoms and physical performance were obtained in all patients. Nonetheless, limb length discrepancy (1–6 cm) was observed in 10 of 14 patients with femoral disease.

Tibia

At variance with femoral MFD, tibial MFD appeared to regularly involve the diaphysis. Three of the four monostotic lesions of tibia were diaphyseal, and one was distal metadiaphyseal. Two of the three diaphyseal lesions appeared as eccentric patches, remained stable over time and required no treatment. In the other patient, a large lytic diaphyseal lesion presented with a pathologic fracture, which was treated with a cast and healed. Ten years later, an extension of the lesion several centimeters above and below the region of fracture was observed. Interestingly, the lesion remained eccentric and cortical, and lytic in character, within the region of secondary extension. The metadiaphyseal lesion progressed over 1 year from a patchy, circumscribed lesion with a sclerotic rind (a patchy lesion) into an extensive involvement of the tibia, from the midshaft through the distal epiphysis. The lesion was complicated by severe varus deformity, 'engraftment' of an aneurysmal bone cyst, a stress fracture, and a 6 cm shortening of the limb. Nonetheless, it remained unfractured. Distraction elongation and internal fixation were employed for treatment with improvement of function.

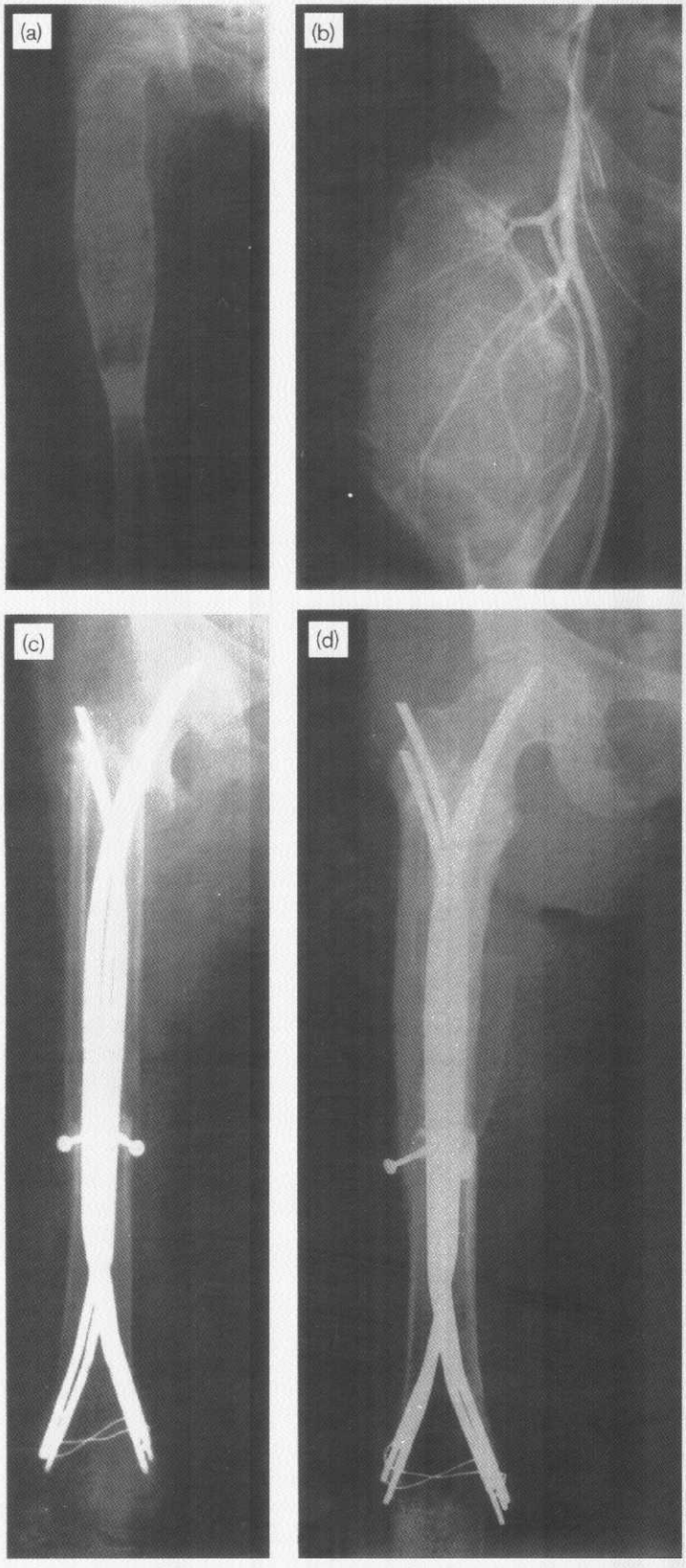
Humerus

Humeral lesions were cystic in radiographic appearance. One lesion, diaphyseal in location, was treated by curettage and CBG following fracture. The lesion did not heal, and indeed showed signs of progression, requiring cortical bone grafting 10 years later. The other lesion was proximal metaphyseal in location, but crossed the physis, which is a relatively unusual occurrence. This lesion was treated by resection, cadaveric bone allograft and internal fixation. Eventual stabilization was achieved for both patients.

Polyostotic fibrous dysplasia

The diagnosis of PFD was confirmed after review of available radiographic and pathological material in a total of 10 patients (Table 4). Four of 10 patients had polymelic involvement with an amphilateral distribution, six of 10 had monomelic PFD. The femur was involved in nine of 10 patients, the tibia in eight of 10, the pelvis in four of 10, the humerus in two of 10, the radius in one of 10, and the fibula in one of 10. Fracture of the femur occurred in four patients, and fracture of the tibia in two. Pathological fracture of the femur was the presenting

Fig. 6



(a) Cervico-diaphyseal, monostotic lesion in the proximal femur of a 9-year old boy. The lesion is markedly expansile and produces a blowout deformity of the bone contour and thinning of the cortex. Note the internal trabecular network on a ground-glass background. (b) Development of a large aneurysmal bone cyst, 2 years later. Note the unusual wealth of vascular supply to the lesional area demonstrated by angiography. (c,d) The lesion was treated by resection and vascularized fibular bone graft and stabilization was achieved by Ender nails and screws.

Table 4 Polyostotic fibrous dysplasia

Patient	Age at diagnosis (years)	Sex	Site	Fracture
1	10	F	Ilium, pubis, femur, tibia, all left	
2	14	M	Femur and tibia, all left	Tibia
3	18	F	Both humeri, right radius	
4	9	M	Ribs (3), right humerus, left femur and tibia	
5	6	F	Right femur, ilium	Femur
6	13	M	Both tibiae, right femur	
7	7	M	Left femur, right femur, tibia and ilium	Femur
8	34	M	Right pelvis, femur, tibia, foot	
9	7	F	Left femur, tibia and fibula	Femur, tibia
10	12	F	Left femur and tibia	Femur

F, female; M, male.

feature in two patients, pain was the initial complaint in all the others. Lower limb length discrepancy (1–4.5 cm) was observed during the course of the disease in six of 10 patients.

Femur

The femur was involved in the upper third in nine of 10 patients. In one of nine, a 'skip' lesion in the distal third was associated with a localized lesion in the upper third. In four of nine, a continuous cervicodiaphyseal lesion was observed. Varus deformity of the femoral neck was present in six patients. In one patient, an unusual valgus deformity of the femoral neck was observed.

Radiographically, a ground-glass pattern was observed in eight cases, occasionally combined with superimposed, minor, lytic or sclerotic features. In one case, the initially ground-glass lesion was seen to acquire a predominantly lytic character over time (Fig. 7). Only one of the observed femoral lesions had a predominantly lytic radiographic appearance at presentation. A patchy appearance similar to a common pattern of MFD was observed in one patient, in whom the diagnosis of FD was made at the age of 35 years, when he developed a stress fracture of the femur (Fig. 8).

Femoral fractures were treated by traction and spica cast in two cases, and by Ender nail fixation in two. In these latter cases, the fracture healed, but coxa vara in both patients (Figs. 7a–c) and valgus deformity of the distal femur in one (not shown), were obvious at follow-up 3 years later. In patients treated with cast, the fractures healed with femoral deformity, which progressed over time and led to corrective surgery in two patients. One had a subtrochanteric osteotomy, curettage and CBG, plus stabilization with a Prevot nail and blade-plate at 7 years of age. Cutting out of the proximal plate required stabilization again with Ender nails and blade-plate 2 years later. Additional subsequent mobilization events ultimately led to removal of hardware and bracing. Deformity and 2 cm limb shortening was the outcome. The other patient developed progressive varus deformity of the femoral neck and valgus deformity of the distal femur, for which osteotomy and blade-plate fixation were performed 12 years after diagnosis at the age of 24 years. The osteosynthesis was stable 7 years after surgery.

Tibia

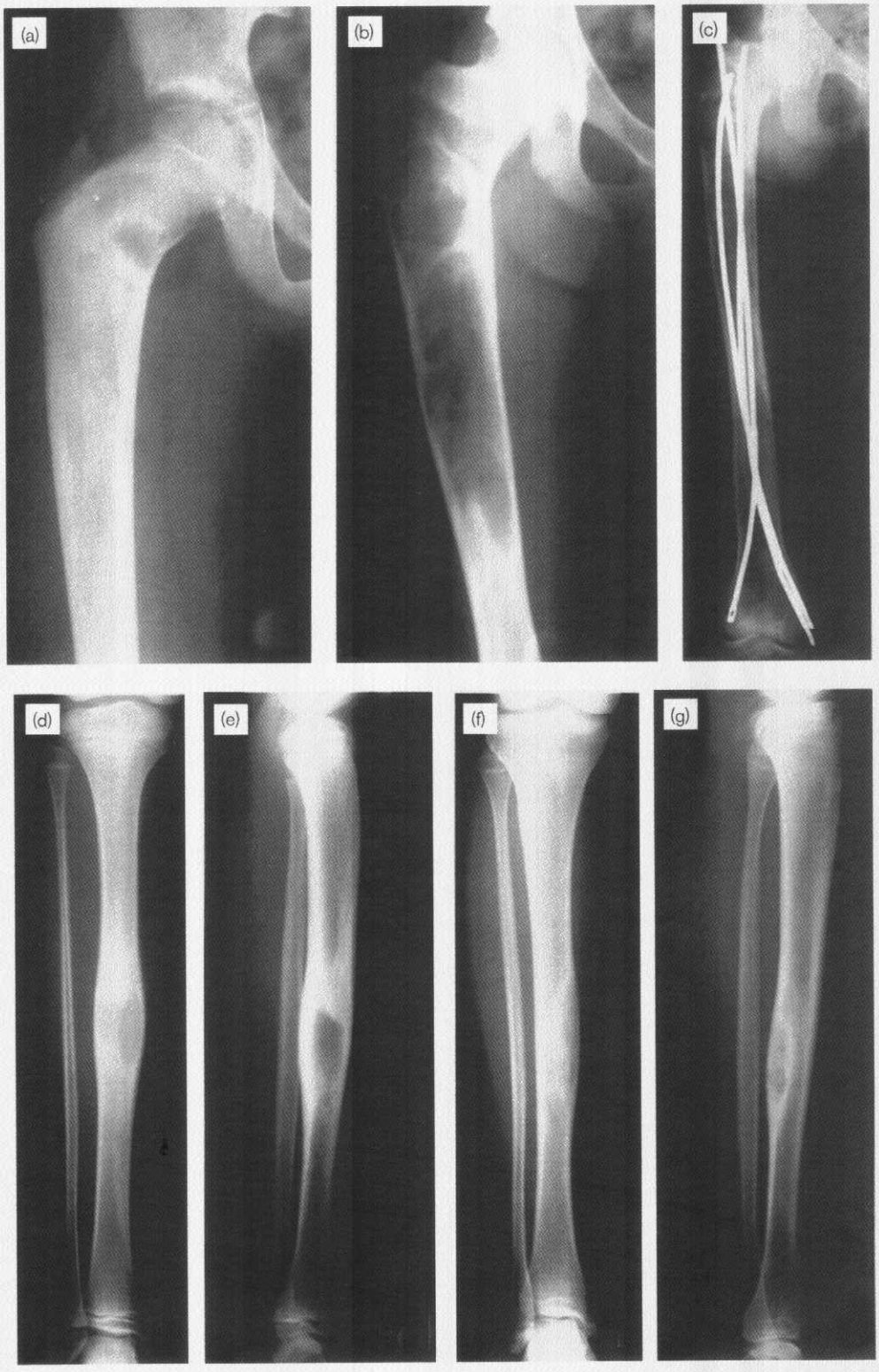
Lesions of the tibia were diaphyseal in four of eight patients, proximal metadiaphyseal in one of eight, and distal metadiaphyseal in two of eight. The predominant initial radiographic appearance (four of eight patients) was that of a single eccentric patchy lesion with combined sclerotic/ground-glass features (Figs. 7d–g). In one of eight cases, a pattern mimicking Brodie's abscess was observed. In one of eight cases, a predominant lytic character was observed which was combined with marked anterior bowing of the tibia. In two of eight patients, multiple and discrete patchy lesions were observed at presentation, and in one of them this picture evolved over time into a diffuse and extensive ground-glass lesion with marked incurvatum deformity.

Fracture of tibia occurred in two of eight patients. In one case (lytic lesion with bowing), it was treated with a vascularized fibular bone graft, which resulted in local healing. A 2.5 cm leg shortening was the ultimate outcome, to which femoral disease also contributed. In the other case (the patient with extensive tibial disease), a recent fracture was treated by intramedullary unreamed tibial nails (UTNs, Synthes-Mathys, Bern, Switzerland). Conservative treatment of unfractured lesions led to an uneventful course of the disease with apparent stabilization over time.

Other bones

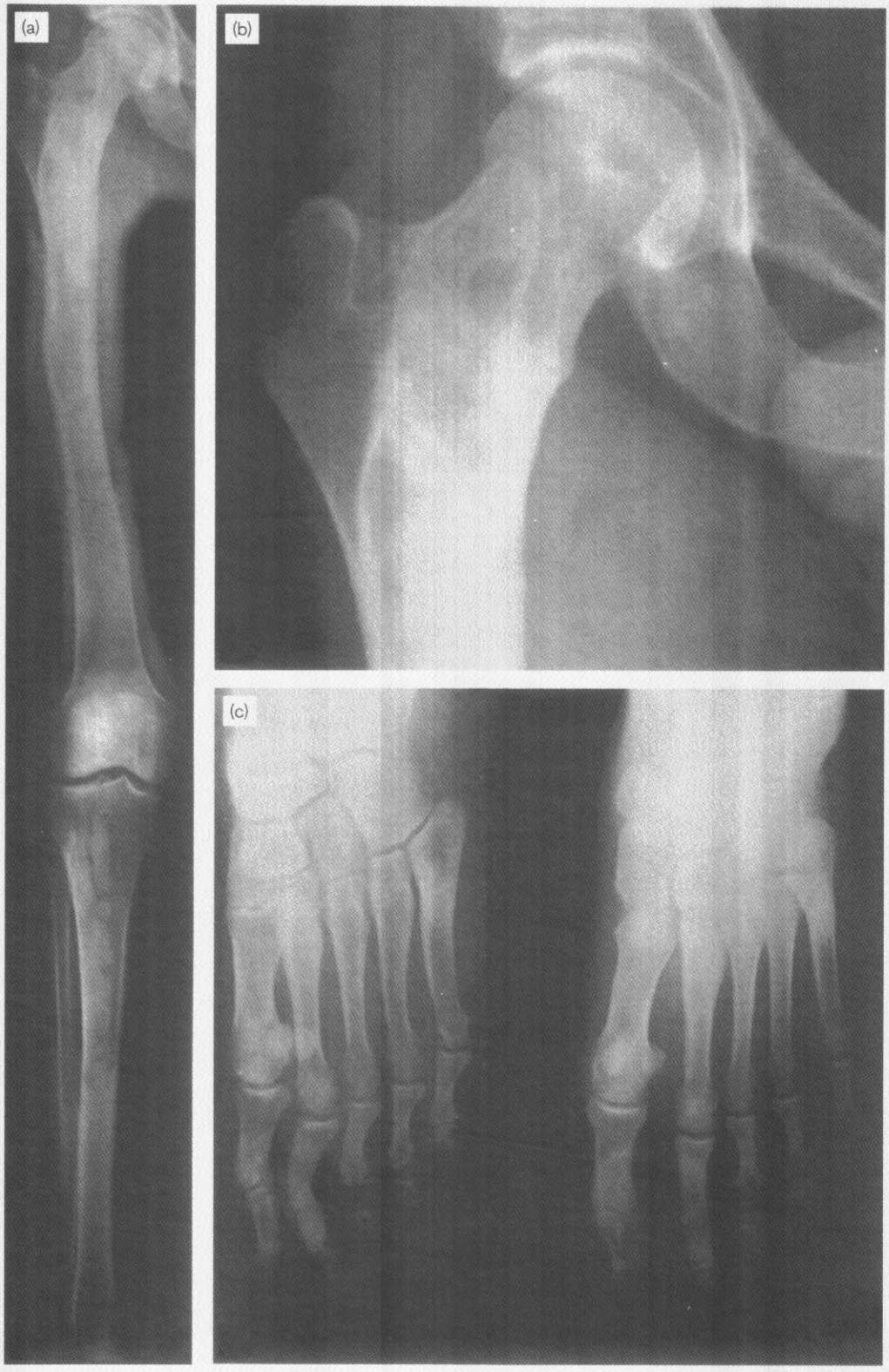
Three humeral lesions were observed in two patients. They were cystic in radiographic appearance (defined as lytic in nature and associated with a localized significant bulging of the bone contour) in two instances, and lytic in another. One cystic lesion was complicated by fracture, which was treated by intramedullary titanium elastic nails (TENs; Synthes-Mathys Medical, Bettlach, Switzerland) with good results. The lesion progressed to a more extensive bone involvement without further events. None of the pelvic lesions required treatment. The lytic humeral lesion was treated by prophylactic TENs (Synthes-Mathys Medical). The single radial lesion and the single fibular lesions were cystic in radiographic appearance and did not cause events. The radial lesion was treated with an intramedullary TEN.

Fig. 7



(a) Extensive cervico diaphyseal lesion in an 8-year old boy. The lesion is predominantly ground glass in appearance with a lytic area. (b) Three years later, the lesion had turned towards a predominantly lytic character, and bone pain had worsened significantly. For this reason, and for the risk of fracture conveyed by the lytic nature of the lesion, three Ender nails were applied. (c) Fifteen years later, the lesion was stable, but a marked coxa vara deformity had developed owing to the lack of stabilization of the neck. (d,e) The tibial lesion was discovered when the patient was 14 years old, was left untreated and (f,g) was stable 12 years later.

Fig. 8



Polyostotic fibrous dysplasia diagnosed at the age of 34 years in a patient who suffered a stress fracture of the femoral neck. (a,b) The lesions are 'patchy' in appearance, both in the femur, where a distinct rind is obvious, and in the tibia, where they are multiple and scattered. (c) Multiple patchy lesions are also present in the short tubular bones of both feet.

Table 5 McCune–Albright syndrome

Patient	Age at diagnosis (years)	Sex	Site	Distribution	Fracture
1	4	F	Femura	A	Yes
2	14	M	Femura, tibia, fibula, pelvis, skull, hands	A	No
3	1	F	Skull, humera, femur, tibiae	A	Yes
4	7	M	Skull, femura, ribs, clavicle, pelvis, humerus	A	Yes
5	6	M	Skull, ribs, humerus, radius, ulna, pelvis, femur, tibia, fibula	I, left	Yes
6	4	F	Skull, jaw, pelvis, femur, tibia, fibula, foot	I, right	Yes
7	3	F	Skull, humeri, radius, ulna, ribs, pelvis, femura, tibiae, fibulae	A	Yes
8	1	F	Skull, humeri, radius, femura, tibia, fibula, scapula, ribs	A	No
9	5	F	Femur, tibia, fibula, foot	I, left	Yes
10	3	M	Skull, ribs, pelvis, humerus, radius, ulna, femura, tibia, fibula	A	Yes
11	3	F	Skull, ribs, pelvis, humerus, radius, ulnae, femura, spine, tibiae, fibulae	A	Yes
12	4	F	Pelvis, femur, tibia, foot	I, left	No
13	4	F	Pelvis, femur, tibia, fibula	I, left	Yes
14	3	M	Skull, femora, spine, legs, pelvis, radius, humeri, hands, feet	A	Yes
15	6	F	Pelvis, femur, tibia, fibula	I, right	Yes
16	6	M	Femur, feet	A	Yes
17	6	F	Skull, ribs, femura, tibia	A	Yes
18	13	M	Femura, tibiae, humeri, radii, ulnae	A	Yes
19	7	M	Skull, humerus, pelvis, femura	A	Yes
20	7	M	Clavicle, humerus, radius, spine, hand, femura, tibiae, feet	A	Yes

F, female; A, amphimetric; M, male; I, ipsilateral.

Table 6 Endocrinopathies and abnormal phosphate metabolism in McCune–Albright syndrome patients

Patient	Endocrinopathies	Phosphaturia
1	PP	No
2	PP, GH excess, ACTH excess	No
3	PP	No
4	Thyroid nodules	No
5	GH excess	No
6	PP, Hyperthyroidism	No
7	PP	Yes
8	Infantile Cushing, PP, thyroid nodules	Yes
9	None	Yes
10	Infantile Cushing, PP, GH excess, thyroid nodules	Yes
11	PP	Yes
12	PP	Yes
13	PP, thyroid nodules	No
14	None	Yes
15	PP, thyroidectomy	No
16	Infantile Cushing (adrenalectomy)	No
17	Multiple, unspecified	No
18	Multiple, unspecified	No
19	Multiple, unspecified	No
20	Multiple, unspecified	No

PP, precocious puberty; GH, growth hormone; ACTH, adrenocorticothrophic hormone.

Table 7 McCune–Albright syndrome and fractures

Patient	Age at fracture (years)	Site of fracture	Number of fractures
1	8	Femur	1
3	Unknown	Femur	Multiple
4	19	Femur	1
5	9,11	Femur	2
6	7,13	Femur	2
7	6–10	Femura	3
		Humerus	2
		Tibia	1
9	11	Femur	1
10	6–17	Femora	Multiple
		Humerus	2
11	6–12	Femora	Multiple
13	8	Femur	1
14	8–14	Humerus	1
		Femora	Multiple
15	Unknown	Femur	Multiple
16	Unknown	Femur	2
17	9–12	Femur	5
18	8–13	Femur	6
19	9	Femur	1
20	8–11	Femur	1
		Cavicle	1
		Radius	1

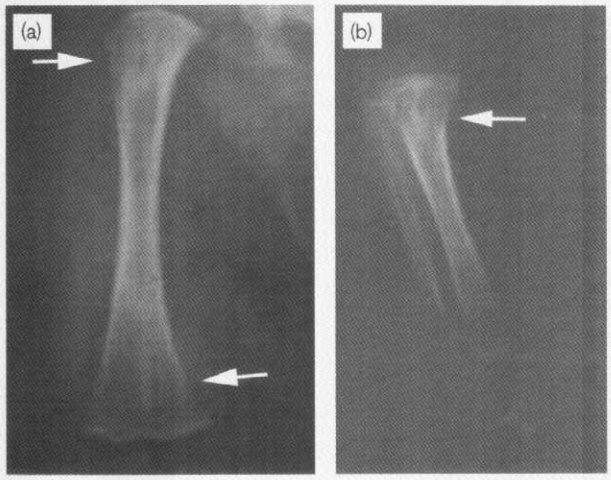
McCune–Albright syndrome

Nineteen of 20 patients in this group displayed the characteristic triad of skin hyperpigmentation, endocrinopathy and bone disease (Table 5). Endocrinopathies (summarized in Table 6) were the presenting clinical features in sixteen of 20 cases. One patient with severe PFD but free of gonadal, thyroid, adrenal or pituitary dysfunction was included in the MAS subset rather than in the PFD subset because of the occurrence of café-au-lait pigmentation and hypophosphatemia with renal phosphate wasting [31].

The skeletal disease was polymelic in all cases, with an ipsilateral distribution in six of 20 and an amphilateral distribution in 14 of 20. Eleven of 14 patients with amphilateral limb disease, and two of six of those with ipsilateral limb disease also had involvement of the craniofacial/axial skeleton.

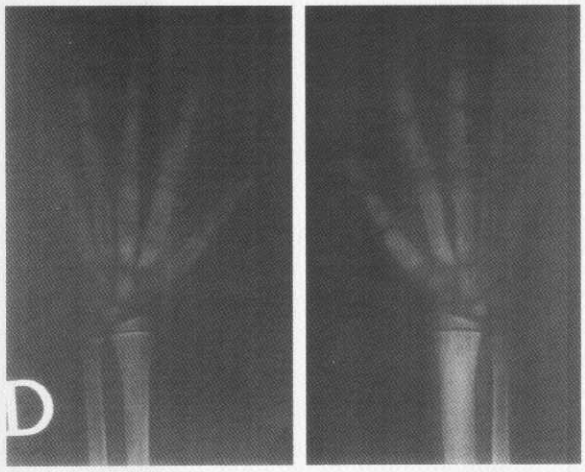
Seventeen of 20 patients experienced at least one fracture, twelve of 20 experienced multiple fractures.

Fig. 9



(a) Femur and (b) tibia of a 2-month-old infant boy. A diagnosis of osteopathia striata was made based on the characteristic features shown (arrows). Compare with Figure 10.

Fig. 10



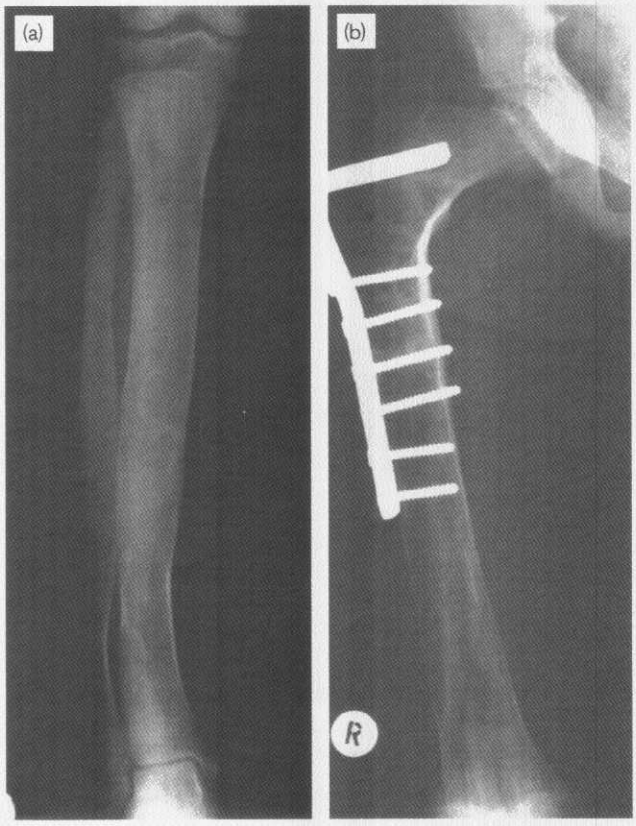
Osteopathia striata in both radio and in short tabular bones of the hand of a 3-year-old patient. Compared with the patient shown in Figure 9, the lesions have a more pronounced sclerotic character, particularly on the right side, reminiscent of melorheostosis. This patient was to develop severe polyostotic fibrous dysplasia.

The peak incidence of first fractures, and of all fractures, occurred between 7 and 12 years of age (Table 7).

Femur

The femur was involved in all patients (20 of 20) and in 17 of them it was involved in its entirety. In the remaining three patients, the disease was localized to the upper third of the femur bilaterally.

Fig. 11

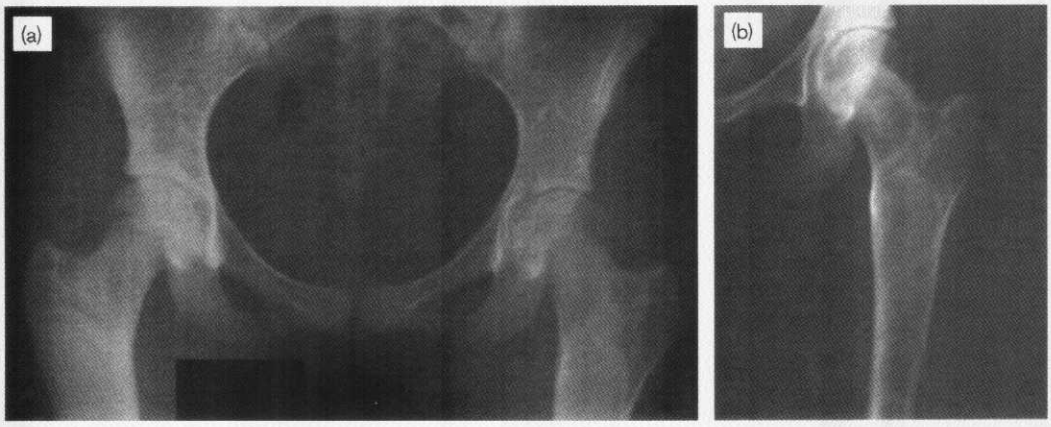


Same patient as in Figure 9 at the age of 13 years. Typical fibrous dysplasia lesions have developed both in the tibia and in the femur.

The usually severe and widespread skeletal involvement in patients with MAS, together with the early onset of endocrinopathies, result in early and repeated medical consultation for this specific subset of patients. For this reason, extensive radiographic material was available for review, with a wide variability of radiographic appearance. For the most part, this expresses the evolution of lesions over a significant time interval (2–40 years of follow-up). A detailed analysis of the available imaging material is in progress but remains beyond the scope of this initial report. Below we briefly describe three general patterns derived from a preliminary analysis, which we feel are important to record as potentially representative of typical landmarks in the evolutionary sequence of FD lesions in the femur, and likely other long bones, in MAS patients.

In the earliest observation in this series, subtle radiographic abnormalities were noted in both femora of a 2-month-old infant. The changes consisted of longitudinal linear densities in the metaphyseal regions, and led to the diagnosis of osteopathia striata (Fig. 9a). Similar features were also observed at the same time in both tibiae of the

Fig. 12



Localized ground-glass lesions in the proximal third of the femur, bilaterally, in a 16-year-old girl with McCune–Albright syndrome.

same patient (Fig 9b), and in the distal radius and in the short tubular bones of the hands of another patient, at the age of 3 years. A more obvious sclerotic character was present in this latter patient's lesions, somewhat reminiscent of melorheostosis (Fig. 10). Over time, typical fibrous dysplasia lesions developed in both patients at the same sites where osteopathia striata had been observed in the earlier radiographs (Fig. 11).

Lesions characterized by an admittedly typical, homogeneous ground-glass appearance were observed in the upper third of the femur, and were accompanied by minimal or no alteration of the bone contour (Fig. 12). These lesions were also free of cystic, lytic or sclerotic features. This pattern was observed in the three patients (age 3–21 years) in the present series whose femoral disease was localized rather than diffuse.

Lesions expanding from the upper third to most of or the entire femur were observed in the vast majority (17 of 20) of cases. The extent of femoral involvement obviously correlated with increasing deformity, expansion of the bone contour, thinning of the cortex, and with the appearance of internal features on the ground-glass background (Fig. 13). These included lytic or cystic changes, trabeculation, and single or multiple sclerotic rims.

Thirteen patients were initially treated conservatively (plaster cast, on occasion with traction) for fracture of the femur. In all of them, the fracture healed with deformity, either as a result of inadequate reduction, or as a secondary evolution towards deformity of fractures that were adequately reduced.

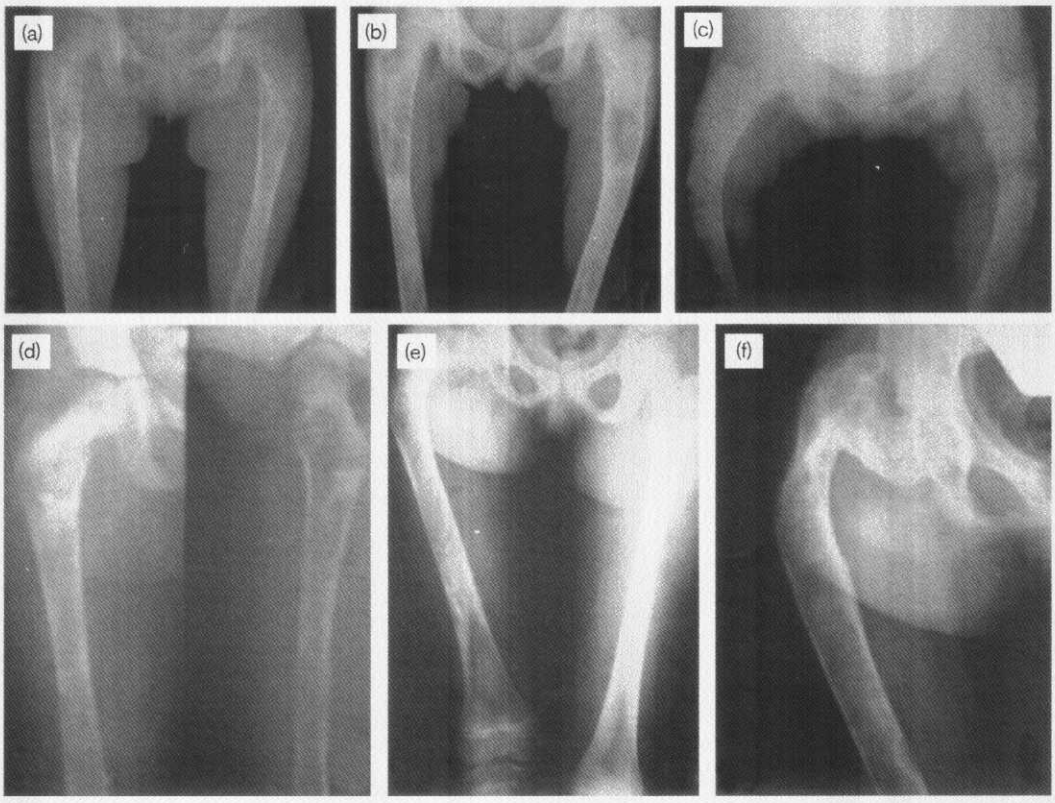
Seven patients were treated with curettage and CBG, which led to resorption of the grafts, relapse and further growth of lesions in all cases.

One patient underwent bilateral femoral lengthening procedures with an Ilizarov apparatus. The procedure failed due to cutting out of the Kirschner wires. The regenerated bone was of poor quality and underwent fracture bilaterally, which required stabilization with peripheral plates. The regenerated bone was clearly fibrous dysplastic at follow-up.

Internal fixation with peripheral plates (either bladeplates, nailplates or sliding screwplates) or screws was used to correct deformity or to fix a fracture in eight patients (14 femurs). The procedure failed in 11 of 14 femurs, resulting in worsening of deformity with or without cutting out, penetration into the hip joint, mobilization, or fracture below the plate (Fig. 14).

Twelve patients (19 femurs) were treated with interlocking cephalomedullary nails: four patients, eight femora with Zickel nails; one patient, two femora with proximal femoral nails (PFNs; Synthes-Mathys, Bettlach, Switzerland); seven patients, nine femora with custom-made unreamed femoral nails-spiral blade (UFN-SBs; Mathys Medical, Bettlach, Switzerland). In all cases, a stabilization of the femur was obtained, with no further fractures, and no worsening of deformity, with a median follow up of 10 years (range 1–20). The growth plates (except the greater trochanter growth plate) were spared in all growing patients, and no growth impairment was observed as a result of the surgery (Figs 15 and 16).

Fig. 13



Progression of femoral disease in two patients (a–c, d–f) with McCune–Albright syndrome. In the first patient, the first radiogram was taken at the age of 4 years, and the last (c) at the age of 11 years. In the second patient, the first at the age of 4 years, the last at the age of 9 years. In both cases, the disease evolves from a ground-glass appearance with minor lytic features and preservation of the bone contour into severe deformity (shepherd's crook), expansion of the bone contour, and clear-cut lytic changes.

Tibia

One tibia was involved in 10 patients, both tibiae in two. The tibia was regularly involved in a diffuse fashion. However, only two fractures of tibia occurred. One was treated conservatively, and healed with deformity requiring subsequent osteotomy and fixation with a plate. The other fracture was treated recently with UTN (Synthes-Mathys) fixation. Surgery for correction of tibial deformity in the absence of fracture was performed in six cases (nine tibiae). A peripheral plate was used in two patients (three tibiae), whereas an intramedullary nail was used in four patients (six tibiae). Good stabilization with an uneventful follow-up was achieved in all cases.

Humerus

One humerus was involved in six patients, both humeri in five. The humeral involvement was diffuse in all cases, with a variable set of secondary changes (cystic, lytic) superimposed on a basic ground-glass background. Three patients experienced a humeral fracture. Two patients were treated with an unreamed humeral nail (UHN; Synthes-Mathys, Bettlach, Switzerland), and one with TENs (Synthes-Mathys Medical) with good results.

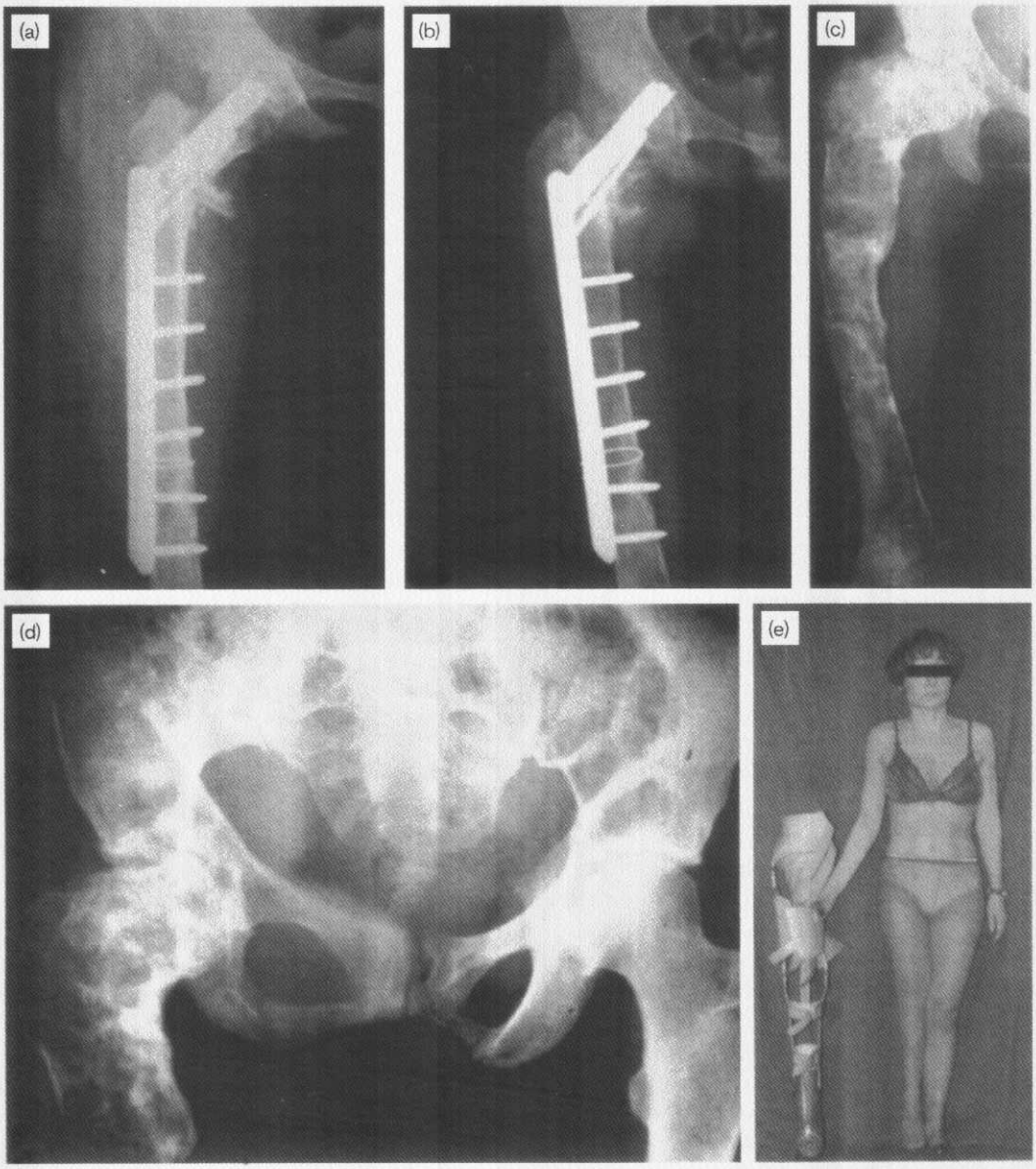
Spine

Involvement of the spine was obvious based on available radiographic and bone scan imaging in three patients. All of them developed a moderate to severe scoliotic curvature. None of them was treated surgically. In another seven patients, a scoliotic curvature was observed in the absence of evidence of FD involvement of the spine (Fig. 17).

Discussion

The present study represents an overview and initial analysis of a large series of cases of FD of bone, occurring either as isolated skeletal disease, or in conjunction with hyperfunctional endocrinopathies in the context of the MAS. We feel that the study has highlighted several specific areas of clinical concern in the diagnosis, management and treatment of the disease as they are itemized below.

Fig. 14

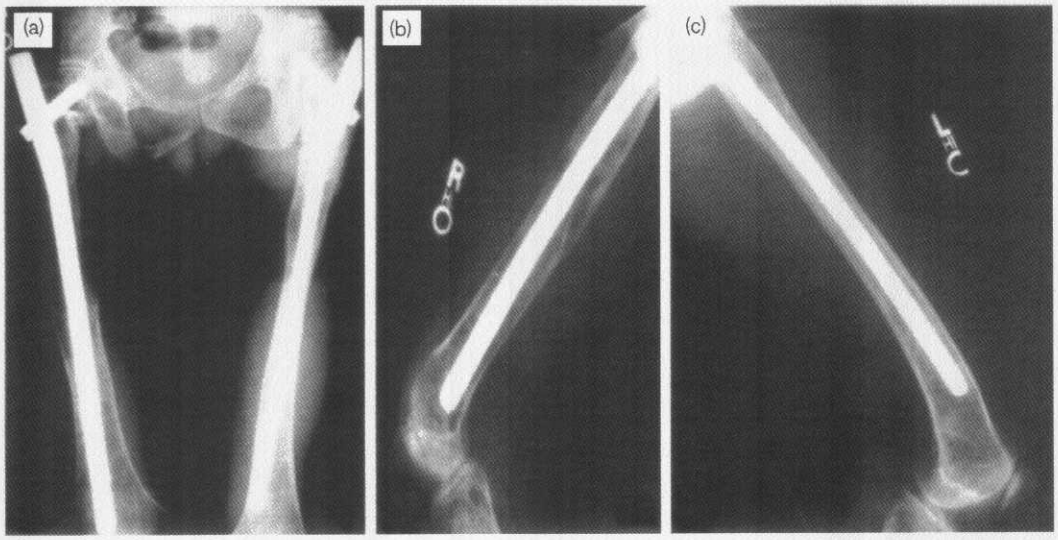


Same patient as in Figure 13d–f. At the age of 10 years, the shepherd crook deformity was corrected by subtrochanteric femoral resection and stabilization with a nail plate. (b) The nail penetrated the hip joint requiring removal 2 months later. (c) At the age of 19 years the femoral disease was associated with hip joint destruction. (d,e) At the age of 45 years the patient is brace-dependent, and has severe osteoarthritis of the hip and marked limb shortening.

Medical evaluation of fibrous dysplasia patients

It should be emphasized that the cases included in this series mostly relate to patients who seek an orthopedic consultation as the first medical opinion. Given the protean way in which the disease may present (also as a result of the potential concurrence of endocrine disorders) a certain bias and inadvertent selection of a specific subset of patients may affect an overall evaluation of the results of the study. For example, involvement of the craniofacial bones may be underestimated in an orthopedic series. We also want to stress that only limited information about concurrent endocrinopathies was available for all patients in this series whose primary diagnosis was MAS, whereas no endocrinological investigation had been conducted in any of the patients whose primary diagnosis was either MFD or PFD. Orthopedic surgeons should be alerted to the need to achieve a thorough medical profile of their FD patients, rather than limiting their attention to acute or elective surgical measures. Hormonal and metabolic imbalances

Fig. 15



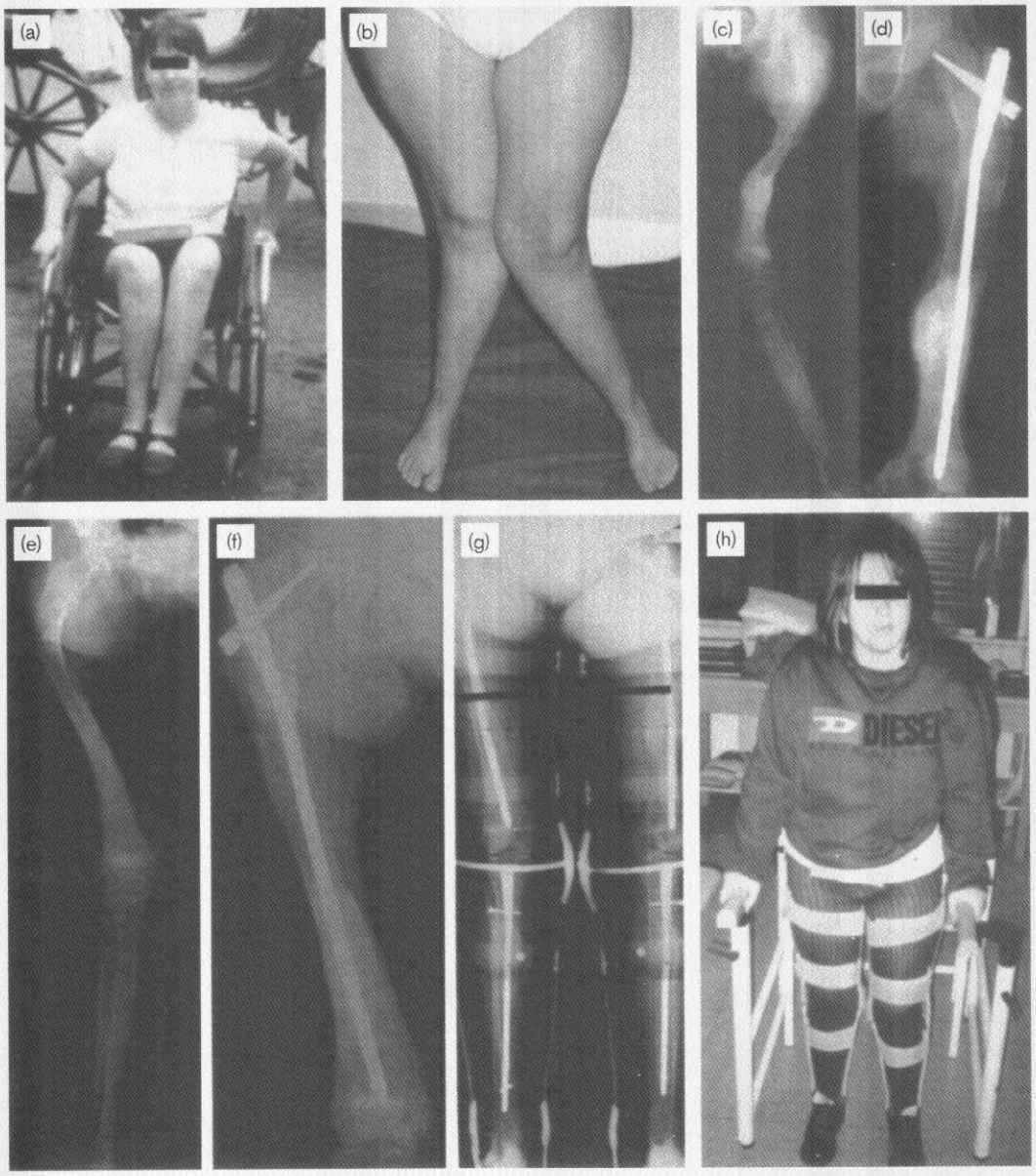
A 33-year-old woman with McCune–Albright syndrome. The patient was operated at the age of 14 years on both femora with osteotomies and insertion of Zickel nails. No mobilization or cutting out of the nails, and no new fractures occurred over almost 20 years after surgery.

accompanying FD [5,32–34] may indeed affect the very nature and evolution of FD lesions, which may reflect on the choice and outcome of surgical procedures. Current appreciation of the specific manner in which metabolic disorders superimpose on the skeletal disease proper remains limited. However, recent data have emphasized, for example, the frequent occurrence of osteomalacic changes within FD lesions, which unavoidably reflect on the compliance of the affected bone, and may depend at least in part on concurrent renal phosphate wasting and hypophosphatemia [16,20,31]. Information on the concurrence of hypophosphatemia with fibrous dysplasia in our series was limited to 16 out of 20 patients with MAS. Renal phosphate wasting and hypophosphatemia occurred in seven of these patients, who suffered an overall minimum 16 fractures (2.2 fractures per patient). Conversely, a total of 13 fractures were recorded for nine patients free of hypophosphatemia (1.4 fractures per patient). Even though a more detailed analysis was not feasible at this time, these observations strongly suggest that hypophosphatemia and renal phosphate wasting may be a significant determinant of the fracture risk in patients with FD. Likewise, many primary (Cushing's syndrome, hyperthyroidism) or secondary (hyperparathyroidism) endocrine imbalances may directly affect bone turnover and mass even within a fibrous dysplastic bone segment [20,35]. The first recommendation emerging from our study is, thus, to pursue a thorough medical evaluation of FD patients at the time of diagnosis. A thorough mapping of the disease by means of bone scans also seems to be often omitted at diagnosis in orthopedic centers, with assessment of the disease being limited in most cases to radiographic study of sites of subjective clinical complaint or functional impairment. A complete assessment of the extent of disease at diagnosis has obvious preventive significance.

Diagnostic pitfalls in monostotic fibrous dysplasia

Two significant implications emerge from the analysis of MFD cases in this series. The first is that initial diagnosis of MFD is very often difficult and uncertain. The high rate of misdiagnosis of MFD that we encountered in the course of this study speaks for the need of careful and interdisciplinary assessment of MFD at first diagnosis. The importance of accurate diagnosis of MFD resides in the implications for follow-up, and for endocrine evaluation, of patients with true MFD. We recommend that histological material, when available, and radiographic films be reviewed by radiologists and pathologists with a specific interest or experience in FD and other skeletal lesions that may mimic FD. We also believe that the initial diagnosis of MFD is perhaps the most important area in which assessment of the specific disease genotype underlying FD has a specific diagnostic significance. Some pitfalls in diagnosis (such as chondroma or angioma, but also osteofibrous dysplasia) are avoided simply by careful histopathology studies, whereas the distinction of genuine FD from other benign fibrous or fibro-osseous lesions (non-ossifying fibromas, ossifying fibromas of jaws, ossifying fibromas of tibia) may require molecular genetics to exclude FD. It is thus recommended that orthopedic surgeons establish proper connections with qualified centers that are equipped for mutation analysis.

Fig. 16

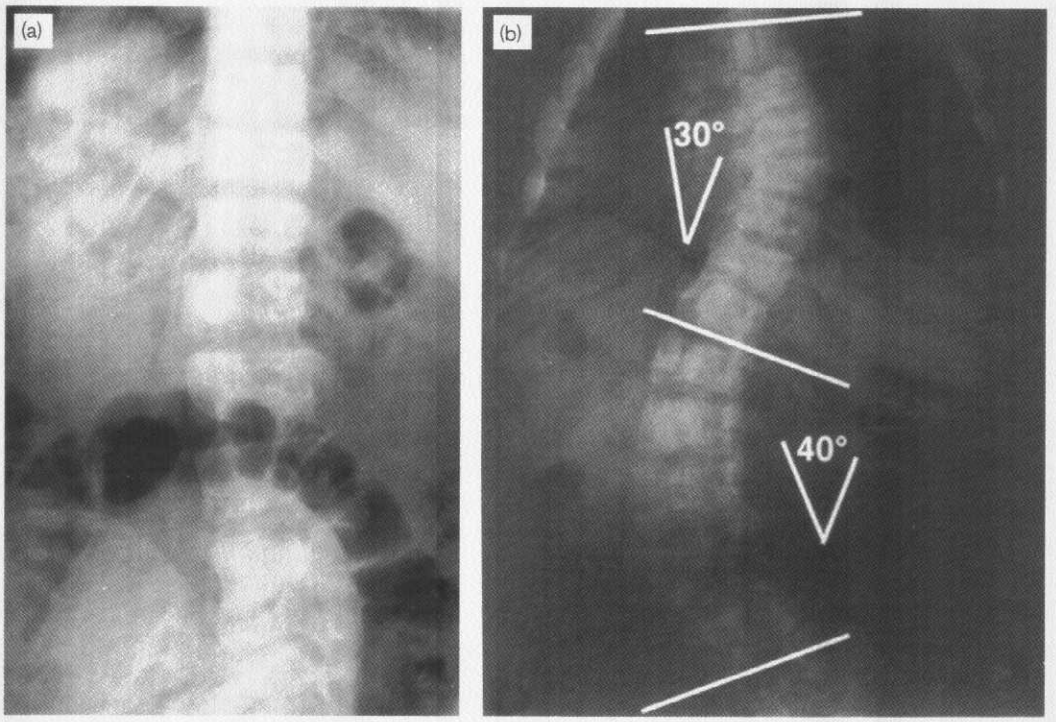


Same patient as in Figure 13a–c. At the age of 13 years, the patient is almost confined to a wheelchair and has severe complex deformity in both femora, compounded by shepherd's crook deformity of the proximal femur, and valgus deformity of the distal femur. Tibiae are also deformed in valgus. The patient was treated with osteotomies and insertion of custom-made unreamed femoral nails and unreamed tibial nails (Synthes-Mathys, Bern, Switzerland), with correction of deformity, and rescue of function.

Lesions mistaken for FD included two broad categories: fibrous or fibro-osseous lesions [36], and non-fibro-osseous lesions such as chondroma/chondromatosis or angioma/angiomatosis [37]. The former category represents pitfalls in radiographic and histopathological evaluation, and the latter category represents pitfalls in radiographic evaluation.

Histopathological criteria outlined in the recent literature (osteoblast cell shape, Sharpey fibers [18,38]) and reviewed elsewhere [20] were found to be useful in discriminating true FD from other benign fibrous or fibro-osseous lesions such as non-ossifying fibroma and osteofibrous dysplasia. Pitfalls in histopathological diagnosis in non-ossifying fibroma may arise from minor events of reactive bone formation at the edges of lesions. The background of the lesion, with typical storiform patterns of fibroblastic cells with no evidence of osteogenesis, and focal collections of foam cells or osteoclasts should be the lead to correct diagnosis. It

Fig. 17



Anteroposterior views of the toracho-lumbar spine of a boy with McCune–Albright syndrome at the age of (a) 10 years and (b) 18 years.

should be remembered, however, that similar patterns may be produced focally in aged FD lesions, and the clinico-radiographic context should be known and considered when evaluating borderline histological specimens.

Osteofibrous dysplasia [39,40] should be easily distinguishable based on radiographic and histological criteria. The distinction is important because it is now clear that the genotype associated with FD (R201 mutations of the GNAS1 gene) is not found in osteofibrous dysplasia [40], which represents a separate entity. Lesional bone trabeculae formed within osteofibrous dysplasia lesions are small, poorly connected, and bordered by morphologically normal osteoblasts, clearly different from the retracted osteoblasts associated with Sharpey fibers seen in FD.

As emphasized in our case of GNAS1 mutation-negative ossifying fibroma of the jaw, which matches a previous report [36], ossifying fibroma of gnathic bones is to be kept separate from cases of mutation-positive FD which may mimic ossifying fibroma both clinically and histologically. Again, the recognition of osteoblasts with normal morphology and of a genuine lamellar structure of most of the lesional bone should point to the possibility that an individual lesion represents ossifying fibroma rather than FD, and indicates the need for genotype analysis.

Fracture risk and progression in monostotic fibrous dysplasia

The other significant lesson derived from the analysis of MFD rests with the apparent conclusion that although limited and bland-looking in most cases, MFD lesions convey a significant risk of fracture (50% of cases in this series), especially in the upper third of the femur. Nonetheless, the manner in which the fracture is treated (traction and cast or internal fixation, eventually associated with curettage and cortical bone grafting) seems to have little impact on the ultimate outcome of the disease, and all eventuate in a satisfactory preservation of function and conformation of the affected limb. This seems to be the result of an inherent limited tendency of most cases of MFD to evolve in an unfavorable fashion. It appears from the present study that most MFD lesions have a very limited tendency to extend over time, or to cause deformity. Lesions more likely to remain stable present as inhomogeneous patches in the upper third of the femur or in the midshaft of the tibia. These lesions may convey a significant risk for

fracture in the femur, but not in the tibia, and may represent low-risk lesions with respect to subsequent deformity or progression. Conversely, cervicodiaphyseal lesions in the femur, distal metadiaphyseal lesions in the tibia, and cystic lesions at any site, may correspond to lesions with a greater tendency to extend and cause secondary events beyond fracture, including deformity, limb shortening, and development of aneurysmal bone cysts.

Orthopedic surgery in polyostotic fibrous dysplasia and McCune–Albright syndrome

Conservative treatment, curettage and CBG, and fixation with screws and plates should all be avoided, based on the analysis of the present series, in the treatment of fractures of the upper third of the femur occurring in the context of PFD and MAS. The inherent tendency for extension and evolution of the FD lesions in these syndromes undermines the success of such procedures. Conservative treatment achieves fracture healing, but the pathological nature of tissue at the fracture site and possible imperfect reduction may cause healing with deformity. Deformity may develop subsequently as a result of disease progression or defective mineralization of the FD bone, and requires additional surgery. CBGs are frequently resorbed, often need to be repeated, do not halt disease progression and do not prevent deformity. Screws and plates frequently cut off and mobilize because of the peculiar compliance of the bony bed in which they are inserted.

Based on the long-term follow-up information from Dr Bray's cases treated with Zickel nails and averaging at present almost 20 years [41], cephalomedullary nailing seems to offer a reasonable option in the surgery of severe femoral FD. This type of surgery provides long-term stabilization of widely affected femora, prevents subsequent fractures and major deformities, and may be used both for treating fractures and as elective surgery. UFN-SBs (Mathys Medical) are interlocking, titanium cephalomedullary nails in which a spiral blade can be inserted into the femoral neck and head, and locking screws into the distal femur. The Zickel nail was the progenitor of these devices and is no longer produced. Regular UFN-SBs currently in use are usually inserted through the *fossa piriformis*, with some inherent damage for the circumflex circulation. The latter is particularly vulnerable, and functionally important, during skeletal growth. For treating current patients seen in Rome and included in the present study, therefore, the UFN-SBs were custom-modified in order to obtain a 7° proximal lateral angulation which allowed insertion through the trochanteric tip and spared the lateral circumflex circulation. Moreover, the proximal part of the nail with its 7° lateral angulation, displaces the proximal fragment medially, with consequent correction of the varus deformity of the femoral neck when the nail is pushed down. A spiral cervical blade interlocked with the nail holds the dysplastic bone of the femoral neck with its large surface, avoiding cutting out of the femoral neck. PFNs (Synthes-Mathys) with two interlocking cephalic screws were used in two cases described above.

Obviously, specific challenges are posed by the need to treat growing children. The obvious care of sparing the growth plates only partially addresses the specific concern. Smaller elastic nails like Ender or TENs (Synthes-Mathys Medical) or Rush pin are not able to prevent either fractures or cervical or diaphyseal deformities and should not be routinely used. Ender or TENs do not prevent refracture, and their use should be limited to particular cases in very young children. They should then be replaced by cephalomedullary nails as soon as allowed by the size attained by the growing femur. Likewise, small intramedullary nails with thin interlocking cervical screws, or without such screws [42], do not seem to provide a long-lasting prophylactic effect against proximal femoral deformity. Ideally, interlocking cephalomedullary nails that can adjust to the geometrical requirements of a growing femur should be designed and can indeed be conceived.

Caveats about the use of plates and screws for treating tibial fractures are less stringent than for the femur. Good stabilization and an event-free follow-up are not infrequent in the present series for patients who received this type of treatment. It should be noted that the tibial disease *per se* diverges from the natural history of proximal femur disease. Mostly diaphyseal and eccentric, tibial lesions jeopardize the mechanical performance much less than proximal femoral lesions, and are associated with a relatively low fracture risk when localized and free of a significant lytic component. Lytic, blown-out, or cystic lesions of tibia, conversely, are of surgical interest whether already complicated by fracture or for the inherent risk for fracture that they convey. In these cases, intramedullary nailing with UTNs (Synthes-Mathys) may be recommended over different types of fixation, considering their predictable stability.

Treatment of humeral fractures in dysplastic areas, or prophylaxis against fracture or deformity in extensive lesions may be performed with either UHNs or TENs (Synthes-Mathys Medical), according to the size of the affected humerus and to the age of the patient. The lower mechanical load on the upper limbs makes smaller devices, like TENs, often suitable for preventing dysplastic bone fracture and deformity in the humerus and forearm bones.

Other orthopedic concerns in polyostotic fibrous dysplasia and McCune–Albright syndrome

The high incidence of scoliosis in patients with MAS seems noteworthy. We observed clinical and radiographic evidence of moderate to severe scoliosis in 50% of these patients, but we obtained direct evidence of vertebral FD only in three of 10. Tissue changes underlying the occurrence of scoliosis, dependent or independent of vertebral FD, remain to be elucidated.

A final remark should be made concerning the high tendency of FD bone to bleed at surgery, which was noted during recent surgeries performed in Rome during the course of this study. When extensive surgery is performed in diffusely involved long bones, mainly when two or three osteotomies are performed to straighten severe deformities, a significant bleeding should be expected. At least three units of blood should be available whenever a cephalomedullary nailing procedure is planned. In tibial osteotomies intraoperative blood loss is scant because ischemic tourniquets are used, but blood loss should be expected after the operation when vacuum drain starts once the tourniquet is released. Grossly, the surgical bed of FD periosteum and bone often resembles a sponge filled with blood. This observation matches our histological experience with the FD lesions, in which markedly dilated and engorged venous channels, and abundant peritrabecular and interstitial microscopic hemorrhage are common findings [20].

References

1 Lichtenstein L. Polyostotic fibrous dysplasia. *Arch Surg* 1938; **36**:874–879.
2 Lichtenstein L, Jaffe HL. Fibrous dysplasia of bone: a condition affecting one, several or many bones, the graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism and still other extraskeletal abnormalities. *Arch Pathol* 1942; **33**:777–797.
3 Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females. *N Engl J Med* 1937; **216**:727–746.
4 Albright F, Scoville B, Sulkowitch HW. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and a gonadal dysfunction: further observations including the report of two more cases. *Endocrinology* 1938; **22**:411–421.
5 Feuillan PP. McCune-Albright syndrome. *Curr Ther Endocrinol Metab* 1997; **6**:235–239.
6 Harris WH, Dudley HR, Barry RJ. The natural history of fibrous dysplasia. *J Bone Joint Surg Am* 1962; **44A**:207–233.
7 McCune DJ, Bruch H. Progress in pediatrics: osteodystrophia fibrosa. *Am J Dis Child* 1937; **54**:806–848.
8 Mazabraud A, Girard J. Un cas particulier de dysplasis fibreuse a localisations osseuses et tendineuses [in French]. *Rev Rhum* 1957; **34**:652–659.
9 Mazabraud A, Semat P, Rose R. A propos de l'association de fibromixomes des tissus mous a la dysplasie fibreuse de l'os [in French]. *Press Med* 1967; **75**:2223–2228.
10 Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. *Proc Natl Acad Sci USA* 1992; **89**:5152–5156.
11 Shenker A, Weinstein LS, Sweet DE, Spiegel AM. An activating Gs alpha mutation is present in fibrous dysplasia of bone in the McCune-Albright syndrome. *J Clin Endocrinol Metab* 1994; **79**:750–755.
12 Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *N Engl J Med* 1991; **325**:1688–1695.
13 Spiegel AM. Inborn errors of signal transduction: mutations in G proteins and G protein-coupled receptors as a cause of disease. *J Inherit Metab Dis* 1997; **20**:113–121.
14 Spiegel AM. The molecular basis of disorders caused by defects in G proteins. *Horm Res* 1997; **47**:89–96.
15 Bianco P, Kuznetsov S, Riminucci M, Fisher LW, Spiegel AM, Gehron Robey P. Reproduction of human fibrous dysplasia of bone in immunocompromised mice by transplanted mosaics of normal and Gs-alpha mutated skeletal progenitor cells. *J Clin Invest* 1998; **101**:1737–1744.
16 Bianco P, Riminucci M, Majolagbe A, Kuznetsov SA, Collins MT, Mankani MH, *et al.* Mutations of the GNAS1 gene, stromal cell dysfunction, and osteomalacic changes in non-McCune-Albright fibrous dysplasia of bone. *J Bone Miner Res* 2000; **15**:120–128.
17 Marie PJ, de Pollak C, Chanson P, Lomri A. Increased proliferation of osteoblastic cells expressing the activating Gs alpha mutation in monostotic and polyostotic fibrous dysplasia. *Am J Pathol* 1997; **150**: 1059–1069.
18 Riminucci M, Fisher LW, Shenker A, Spiegel AM, Bianco P, Gehron Robey P. Fibrous dysplasia of bone in the McCune-Albright syndrome: abnormalities in bone formation. *Am J Pathol* 1997; **151**:1587–1600.
19 Shenker A, Chanson P, Weinstein LS, Chi P, Spiegel AM, Lomri A, Marie PJ. Osteoblastic cells derived from isolated lesions of fibrous dysplasia contain activating somatic mutations of the Gs alpha gene. *Hum Mol Genet* 1995; **4**:1675–1676.
20 Bianco P, Gehron Robey P, Wientroub S. Fibrous dysplasia of bone. In: Glorieux HJ (editor): *Pediatric bone biology and disease*. New York: Academic Press; (in press).
21 Dorfman HD, Czerniak B. *Bone tumors*. St. Louis: Mosby; 1997.
22 Andrisano A, Soncini G, Calderoni PP, Stilli S. Critical review of infantile fibrous dysplasia: surgical treatment. *J Pediatr Orthop* 1991; **11**:478–481.
23 Enneking WF, Gearen PF. Fibrous dysplasia of the femoral neck. *J Bone Joint Surg Am* 1986; **68A**:1415–1422.
24 Guille JT, Kumar SJ, MacEwen GD. Fibrous dysplasia of the proximal part of the femur. *J Bone Joint Surg Am* 1998; **80A**:648–658.
25 Kumta SM, Leung PC, Griffith JF, Kew J, Chow LTC. Vascularized bone grafting for fibrous dysplasia of the upper limb. *J Bone Joint Surg Br* 2000; **82B**:409–412.
26 Stephenson RB, London MD, Hankin FM, Kaufer H. Fibrous dysplasia. *J Bone Joint Surg Am* 1987; **69A**:400–409.
27 Chapurlat RD, Delmas PD, Liens D, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *J Bone Miner Res* 1997; **12**:1746–1752.
28 Lala R, Matarazzo P, Bertelloni S, Buzi F, Rigon F, de Sanctis C. Pamidronate treatment of bone fibrous dysplasia in nine children with McCune-Albright syndrome. *Acta Paediatr* 2000; **89**:188–193.
29 Liens D, Delmas PD, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *Lancet* 1994; **343**:953–954.
30 Zacharin M, O'Sullivan M. Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome. *J Pediatr* 2000; **137**:403–409.
31 Collins MT, Chebli C, Jones J, Kushner H, Consugar M, Rinaldo P, *et al.* Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. *J Bone Miner Res* 2001; **16**:806–813.
32 Akintoye S, Chebli C, Booher S, Feuillan P, Kushner H, LeRoith D, *et al.* Characterization of gsp-mediated growth hormone excess in the context of McCune-Albright Syndrome. *J Clin End Metab* 2002; **87**: 5104–5112.
33 Chanson P, Dib A, Visot A, Derome PJ. McCune-Albright syndrome and acromegaly: clinical studies and responses to treatment in five cases. *Eur J Endocrinol* 1994; **131**:229–234.
34 Feuillan PP. McCune-Albright syndrome. *Curr Ther Endocrinol Metab* 1994; **5**:205–209.
35 Corsi A, Collins MT, Mankani MH, Gehron Robey P, Bianco P. Core biopsy studies of fibrous dysplasia of bone: evidence for impaired mineralization of lesional bone and for hormonal dependency of turnover within the lesion [Abstract]. *J Bone Min Res* 2000; **15S**:485.
36 Riminucci M, Collins M, Corsi A, Boyde A, Murphey MD, Wientroub S, *et al.* Gnatho-diaphyseal dysplasia: a syndrome of fibro-osseous lesions of jawbones, bone fragility, and long bone bowing. *J Bone Miner Res* 2001; **16**:1710–1718.

37 Collins MT, Riminucci M, Corsi A, Murphey MD, Wientroub S, Bianco P, Gehron Robey P. Angiomatosis of bone with localized mineralization defect. *J Bone Miner Res* 2001; **16**:1750–1753.

38 Riminucci M, Liu B, Corsi A, Shenker A, Spiegel AM, Gehron Robey P, Bianco P. The histopathology of fibrous dysplasia of bone in patients with activating mutations of the Gs alpha gene: site-specific patterns and recurrent histological hallmarks. *J Pathol* 1999; **187**: 249–258.

39 Park YK, Unni KK, McLeod RA, Pritchard DJ. Osteofibrous dysplasia: clinicopathologic study of 80 cases. *Hum Pathol* 1993; **24**: 1339–1347.

40 Sakamoto A, Oda Y, Iwamoto Y, Tsuneyoshi M. A comparative study of fibrous dysplasia and osteofibrous dysplasia with regard to Gs alpha mutation at the Arg201 codon: polymerase chain reaction-restriction fragment length polymorphism analysis of paraffin-embedded tissues. *J Mol Diagn* 2000; **2**:67–72.

41 Freeman BH, Bray EW, Meyer LC. Multiple osteotomies with Zickel nail fixation for polyostotic fibrous dysplasia involving the proximal part of the femur. *J Bone Joint Surg Am* 1987; **69A**:691–698.

42 O'Sullivan M, Zacharin M. Intramedullary rodding and bisphosphonate treatment of polyostotic fibrous dysplasia associated with the McCune-Albright syndrome. *J Pediatr Orthop* 2002; **22**:255–260.